REMARKS

Claims 200-298 are pending. Claims 200-247, 252-257, 260-282, and 287-292 are under examination. Claim 200 has been amended to insert a term inadvertently omitted from the claim. Support for the amendment can be found throughout the specification and the claims as filed, in particular in original claim 7. Accordingly, this amendment does not raise an issue of new matter and entry thereof is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

The rejection of claims 200-212, 214-226, 228-241, 243-247, 252-257, 260-276, 278-282 and 287-292 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description is respectfully traversed. Applicants respectfully maintain, for the reasons of record, that the specification provides sufficient description and guidance for the claimed peptides and conjugates.

As discussed in the previous responses filed September 18, 2006, and August 20, 2007, Applicants respectfully maintain that the specification teaches a peptide "comprising" CREKA (SEQ ID NO:1). In particular, the CREKA peptide was identified using a phage display library that was injected into mice and recovered from breast tumor tissue (Example 1, pages 67-70). A peptide library was used, with the peptide expressed on the surface of the phage as a fusion with a phage protein, in particular the product of gene III. Such a peptide-gene III fusion protein is exemplary of a peptide "comprising" CREKA.

Regarding the recited size limitations and functional activity, Applicants respectfully maintain that the claims do not include non-functional variants but only those peptides or conjugates comprising CREKA that have a length of less than 100 residues and that selectively home to tumor vasculature or selectively bind collagen. Thus, the claims are directed to peptides and conjugates and specifically recite size limitations, having a length of less than 100 residues or shorter recited sizes, and functional activity, selectively homing to tumor vasculature or selectively binding collagen, of the peptides comprising CREKA.

As discussed in the previous response, Applicants respectfully maintain that it is well known to the skilled artisan how to add amino acids to the amino- or carboxyl-terminus of a

CREKA peptide and test the ability of the peptide to selectively home to tumor vasculature or selectively bind collagen using, for example, the methods taught in the specification (see Examples 1-3, pages 67-78). As an example, the CREKA peptide of SEQ ID NO:1 is a 5 amino acid sequence, or "5-mer" peptide. Claim 212 recites that the peptide has a length of less than 7 residues, and one skilled in the art would readily know how to add a single amino acid on the amino- or carboxyl-terminus of SEQ ID NO:1 using routine and well known methods in order to obtain a 6 amino acid peptide "comprising" SEQ ID NO:1. Such a 6-mer peptide can be readily tested for selective homing to tumor vasculature or selective binding to collagen using methods as taught in the specification and well known to those skilled in the art (see Examples 1 and 3). Similarly, claim 211 recites that the peptide has a length of less than 8 residues. One skilled in the art would readily know how to add a single amino acid on the amino- and carboxyl-termiums of SEQ ID NO:1, or add two amino acids on the amino-terminus or two amino acids on the carboxyl-terminus, in order to obtain a 7-mer peptide "comprising" SEQ ID NO:1. Again, routine methods can be used to test for selective homing to tumor vasculature or selective binding to collagen. Moreover, it would be routine to add further amino acids to a peptide "comprising" SEQ ID NO:1, including sufficient amino acids to provide a peptide having a length of less than 100 residues, and test for functional activity of selective homing to tumor vasculature or selective binding to collagen.

Furthermore, as discussed above and in the previous responses filed September 18, 2006, and August 20, 2007, the specification teaches that the peptides were identified as tumor homing molecules using phage display, in which a peptide library was expressed as a fusion protein on the surface of a phage (see Examples 1 and 2, pages 67-72). Thus, the CREKA peptide was identified as a tumor homing peptide comprising the phage coat protein to which the peptide was fused and therefore exemplifies a peptide "comprising" the recited CREKA peptide sequence that selectively homes to tumor vasculature or selectively binds collagen.

The Office Action asserts that "the skilled artisan could not envision the detailed chemical structure(s) of the encompassed genus of a homing peptides or conjugates having less than 7, 8, 9, 10, 12, 15, 20, 25, 30, 35, 40, 50, or 100 amino acid residues comprising CREKA peptide (SEQ ID NO: 1), which could maintain the same functiona [sic] as CREKA. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity

or simplicity of the method of isolation." The Examiner's reliance on citations to *University of California v. Eli Lilly & Co.,* 119 F.3d 1559 (Fed.Cir.1997) and *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed.Cir.1993) is misplaced. In both cases, the patent specifications at issue did not identify the sequence (structure) of any embodiment of DNA claimed therein. See *Eli Lilly*, 119 F.3d at 1567-68 (affirming a judgment that the claim requiring cDNA encoding human insulin was invalid for failing to provide an adequate written description where the specification described the human insulin A and B chain amino acid sequences encoded by the cDNA, but did not provide the nucleotide sequence for the cDNA itself); *Fiers*, 984 F.2d at 1167-68, 1170-71 (finding the written description insufficient where the patent claimed purified DNA encoding human fibroblast interferon-beta polypeptide, but the specification only disclosed a bare reference to DNA and suggested a process to sequence it).

Applicants respectfully disagree with the assertion in the Office Action on page 4 that "[T]he instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features and representative number of the species that are common to the genus of homing peptides (less than 6-100 residues) comprising sequence CREKA (SEQ ID NO: 1), which homes to tumor vasculature and selectively binds to collagen." To the contrary, the definitive structural feature is the CREKA sequence, which is specifically recited in the claims and has the functional activity of selectively homing to tumor vasculature and selectively binding to collagen. Thus, contrary to the assertion in the Office Action, the claims specifically recite the common attribute or characteristic that identifies members of the genus associated with the activities recited in the claims, namely the CREKA sequence. Moreover, the structural feature of the CREKA sequence is common to all members of the claimed genus of peptides comprising CREKA. Thus, Applicants have provided a structural feature and correlated it with a functional activity. The written description requirement as articulated by the Federal Circuit and adopted by the PTO requires no more. In *Enzo Biochem v. Gen-Probe, Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) ("Enzo II"), the Federal Circuit stated that "the written description requirement would be met for all of the claims [of the patent at issue] if the functional characteristic of [the claimed invention was] coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. This standard annunciated by the Federal Circuit was adopted and incorporated into the PTO guidelines, which state that the written description requirement of 35 U.S.C. § 112, ¶ 1, can be met by

> show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or **partial structure**, other physical and/or chemical properties, functional characteristics when **coupled with a known or disclosed correlation between function and structure**, or some combination of such characteristics.

Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph, "Written Description" Requirement, 66 Fed.Reg. 1099, 1106 (Jan. 5, 2001) (emphasis supplied).

As discussed above, Applicants respectfully submit that one skilled in the art could readily envision a peptide comprising CREKA having a length of less than 7, 8, 9, 10, 12, 15 residues, and so forth, up to a length of less than 100 residues. Second, contrary to the assertion in the Office Action, Applicants respectfully submit that the claims were reduced to practice, as described in the working examples where selective homing to tumor vasculature and selective binding to collagen were demonstrated for the CREKA sequence (see Examples 1 and 3). Therefore, Applicants respectfully submit that, based on the teaching in the specification, one skilled in the art could readily envision the claimed genus of peptides comprising CREKA having a length of less than 100 residues. The Federal Circuit has held that the disclosure of a single genetically-engineered functional variant of a known protein was sufficient to provide adequate written description to support a claim encompassing essentially any engineered variant of the protein sharing the modified function. *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052 (Fed. Cir 2005).

Regarding the response to Applicants' arguments as set forth in the Office Action on pages 7-9, the Office Action asserts that the claims encompass a genus that is "highly variant." However, there is no variation of the specifically recited structural motif, namely the CREKA sequence, that has the functional activity of selectively homing to tumor vasculature and selectively binding to collagen. As demonstrated in the working examples, the CREKA sequence is sufficient to selectively home to tumor vasculature and selectively bind collagen (see Examples 1 and 3), and the CREKA sequence is common to all members of the genus of peptides comprising CREKA and having a length of less than 100 residues.

With respect to the comments in the Office Action on the Smith et al. reference, Chem. Rev. 97:391-410 (1997), and phage display, Applicants' previous response and comments were

directed to clarifying the record and Applicants' position that the Smith et al. reference was mischaracterized in the previous Office Action. In the present Office Action on page 9 (first complete sentence), it is stated that "regarding with the teaching of Smith et al on phage display more than 8 amino acids supplemented by wild type pVIII molecules, instant specification does not provide clear information that in the process of screening the tumor homing molecule or collagen binding molecule wild type pVIII molecule was supplemented, and no more than 8 amino acids of the homing molecules were identified in this application." Applicants respectfully request clarification as to what significance any lack of description in the specification of wild type pVIII molecules being supplemented has to do with the gene III fusions exemplified in Example 1 in which the CREKA peptide was identified by phage display and shown to have the claimed functional activity of selectively homing to tumor vasculature and selectively binding to collagen.

To again clarify the record, the statement in the Office Action mailed February 20, 2007, reads as follows: "[I]n addition, Smith et al. (Chem Rev, vol 97, page 391-410) teach phage display system for screening a peptide comprising homing molecule and indicate when the gene display a relative large foreign peptide (more than eight amino acids), it will not support phage production and produce mosaic particles (page 393, col 2)" [emphasis in original]. As stated in the previous response filed August 20, 2007, this statement in the previous Office Action is a mischaracterization of Smith et al., which reads as follows on page 393, column 2:

> In some pIII vectors, the foreign peptide replaces the N-terminal domain of pIII (the third diagram in Figure 1), yielding a hybrid protein that can be incorporated into the virion but must be supplemented by complete pIII molecules if the virion is to be infective (see type 3+3 systems in the next subsection); infective virions in this case are thus mosaics with two types of pIII molecule. Similarly, when pVIII displays a relatively large foreign peptide (more than about eight amino acids), it will not support phage production unless it is supplemented by wild-type pVIII molecules, again yielding mosaic particles.

The present Office Action now appears to set forth that supplementation of pVIII and the lack of such disclosure in Applicants' specification is an apparent justification of the previous mischaracterization of Smith et al., as if Applicants need to prove the teachings of Smith et al. that larger peptides can in fact be expressed in phage, as pointed out in the previous response and described in Table 1 of Smith et al. Smith et al.

describes the known art of phage display and to suggest that Applicants' specification does not provide teachings that Smith et al. is correct in its description of larger peptides being capable of display on phage is misplaced. The specification need not disclose and preferably omits that which is well-known to those skilled in the art and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). Therefore, it is unclear how Applicants' comments on Smith et al. justify the position set forth in the Office Action in the first complete sentence on page 9.

The Office Action on page 9 further asserts that "[A]lthough functional language is limited [to the] claimed peptide bound to collagen or homing to the tumor vasculature, the peptide could extend about 20 times of functional peptide CREKA in its length, which could include an known or unknown collagen binding or tumor homing motif which is not invented by applicant. In another word, the collagen binding or homing of claimed peptides may not be contributed by CREKA sequence in thhis [sic] case." Applicants respectfully submit that any contribution of other activities of a sequence "comprising" CREKA is irrelevant, the only relevant issue being whether the CREKA structure specifically recited in the claims has the recited functional activity of selectively homing to tumor vasculature or selectively binding to collagen and that the peptide comprising CREKA has the functional activity recited in the claims.

For the reasons of record and as discussed above, Applicants respectfully maintain that the specification provides sufficient description and guidance for the claimed peptides and conjugates. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

The rejection of claims 200-212, 214-226, 228-241, 243-247, 252-257, 260-276, 278-282 and 287-292 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is

respectfully traversed. Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed peptides and conjugates.

The Office Action asserts on page 6 that the "specification does not teach any peptide at any length (7-100 amino acids) comprising CREKA would retain the activity of binding to collagen and homing to tumor vasculature" [emphasis in original]. Applicants respectfully disagree with this assertion. As discussed above and in the previous response, the specification teaches that the peptides were identified as tumor homing molecules using phage display, in which a peptide library was expressed as a fusion protein on the surface of a phage (see Examples 1 and 2, pages 67-72). Thus, the CREKA peptide was identified as a tumor homing peptide comprising the phage coat protein to which the peptide was fused and therefore exemplifies a peptide "comprising" the recited CREKA peptide sequence that selectively homes to tumor vasculature and selectively binds collagen, as recited in the claims.

Regarding the recited size limitations and functional activity, as discussed above, Applicants maintain that the claims do not include non-functional variants but only those peptides or conjugates comprising CREKA (SEQ ID NO:1) that have a length of less than 100 residues and that selectively home to tumor vasculature or selectively bind collagen. The Office Action states on page 6:

> It is well known in the art that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6. 1).

Mathews and Van Holde is a biochemistry textbook, and the cited pages fall under the chapter entitled "The Three-dimensional Structure of Proteins." Applicants respectfully maintain, as discussed in the previous response filed August 20, 2007, that the folding of proteins into a 3-dimensional structure, as discussed in Mathews and Van Holde, is not relevant to the claimed peptides and conjugates, in which the functional activity of the CREKA peptide of selectively homing to tumor vasculature and selectively binding to collagen is recited in the claims. With respect to the possibility of a claimed peptide comprising CREKA folding into a 3-dimensional structure, the claims recite a size limitation for the peptides, which in the case of the largest

peptide has a length of less than 100 residues. For example, in the case of claim 212, the peptide has a length of less than 7 residues, and such a peptide would not be expected to fold into a 3-dimensional structure, and similarly with a length of less than 8 residues, less than 9 residues, and so forth, up to the size of a peptide that would be capable of folding into a 3-dimensional structure. Moreover, even if, *arguendo*, a particular peptide "comprising" CREKA and having a length of less than 100 residues were to be able to fold into a 3-dimensional structure that was inactive with respect to selectively homing to tumor vasculature or selectively binding to collagen, such a peptide would not be encompassed by the claims, which require that the peptides and conjugates have the recited functional activity of selectively homing to tumor vasculature or selectively binding to collagen.

As discussed in the previous response, Applicants respectfully maintain that Burgess et al., J. Cell Biol. 111:2129-2138 (1990), and Lazar et al., Mol. Cell. Biol. 8:1247-1252 (1988), at best, appear to describe amino acid substitutions of the binding site of acidic fibroblast growth factor (FGF) or transforming growth factor α (TGFα), respectively (see abstract of both references). In contrast, the claimed peptides and conjugates recite the CREKA sequence and require the functional activity of the CREKA peptide of selective homing to tumor vasculature or selective binding to collagen. Accordingly, Applicants respectfully submit that the description in Burgess et al. and Lazar et al. of amino acid substitutions in the binding site of acidic FGF and TGFα that alter activity are not relevant to the claimed peptides and conjugates, which recite the CREKA peptide that has the functional activity of selectively homing to tumor vasculature or selectively binding collagen.

Regarding the Shimkets et al. reference, WO 2001/192523, the Office Action asserts that this reference describes a peptide comprising CREKA but does not record the peptide as having the function of homing to tumor vasculature and binding to collagen. Applicants respectfully maintain, as discussed in the previous response filed August 20, 2007, that the assertion in Shimkets et al. that the 11,491 open reading frames identified can be used in the treatment of a laundry list of diseases and conditions is not relevant to the claimed peptides, which recite the specific structure of the CREKA peptide and the functional activity of selectively homing to tumor vasculature and selectively binding collagen. In the present Office Action on page 7, it is asserted that "one skilled in the art has not recognized a peptide having less than 100 amino acids

at length comprising amino acids CREKA would bind to a collagen and homing to tumor because treating disease like neurodegenerative disease do not require binding or homing to tumor vascular [sic]." A lack of correlation between treating a neurodegenerative disease and homing to tumor vasculature is completely irrelevant to the claimed peptides, which have the recited functional activity of selectively homing to tumor vasculature or selectively binding collagen, not treating a neurodegenerative disease.

As discussed above, Applicants respectfully maintain that it is well known to the skilled artisan how to add amino acids to the amino- or carboxyl-terminus of a CREKA peptide and test the ability of the peptide to selectively home to tumor vasculature and selectively bind collagen using, for example, the methods taught in the specification (see Examples 1-3, pages 67-78). Furthermore, as discussed above, the specification teaches that the peptides were identified as tumor homing molecules using phage display, in which a peptide library was expressed as a fusion protein on the surface of a phage (see Examples 1 and 2, pages 67-72). Thus, the CREKA peptide was identified as a tumor homing peptide comprising the phage coat protein to which the peptide was fused and therefore exemplifies a peptide "comprising" the recited peptide CREKA sequence that selectively homes to tumor vasculature and selectively binds collagen, as recited in the claims. Accordingly, Applicants respectfully maintain that one skilled in the art would readily understand how to make and use the claimed peptides "comprising" CREKA (SEQ ID NO:1) because it would be routine to make peptides comprising CREKA and having a length of less than 100 amino acids and to test for the recited activities of selectively homing to tumor vasculature and selectively binding collagen, as recited in the claims.

The Office Action additionally asserts on page 6 that the "specification does not provide any working example or guideline, which enable any conjugate of therapeutic agent linked to the peptide above comprising CREKA (SEQ ID NO: 1) in the claims, which could binds to collagen, or homes to tumor vasculature and maintain the therapeutic function. Thus, one skilled in the art would not know how to use or even make a peptide based on the claims for tumor vasculature homing and binding to collagen without undue experimentation." Applicants respectfully disagree with this assertion and maintain that one skilled in the art would readily know how to make and use a peptide or conjugate comprising the CREKA peptide. As discussed above, the specification teaches that the CREKA peptide was identified using phage display, demonstrating

that a CREKA peptide comprising additional sequence and including a bulky moiety such as a phage can selectively home to tumor vasculature and selectively bind collagen (see Examples 1 and 3). The specification further teaches a variety of moieties that can be included in a conjugate with a CREKA peptide for selectively homing to tumor vasculature or selectively binding to collagen, including therapeutic moieties (page 37, line 3, to page 38, line 16, and page 46, line 17, to page 60, line 8). Based on the teaching in the specification and what was well known in the art, one skilled in the art could readily make and use a peptide or conjugate comprising the CREKA sequence, as claimed.

Regarding the response to Applicants' arguments as set forth in the Office Action on pages 9-11, Applicants respectfully maintain, as discussed above and in the previous response, that the specification provides sufficient description and guidance for the claimed peptides and conjugates comprising CREKA. The Office Action asserts that Applicants do not seem to be concerned with the secondary structure of the fusion (pIII fusion on the phage). However, as discussed above and in the previous response, secondary structure of any peptide comprising CREKA encompassed by the claims is not an issue since a peptide of the claims either has no secondary structure or has secondary structure that permits the functional activity of selectively homing to tumor vasculature and selectively binding to collagen.

The Office Action further discusses that one skilled in the art, including the inventor, have "published homing molecules for years and most of the molecules are small peptides with less [than] about 10 amino acids for maintaining the specificity of the tumor vascular homing ability." Applicants respectfully request that the Examiner provide evidence that a size of less than about 10 amino acids is required to maintain the specificity of the tumor vasculature homing activity of the peptides. The fact that small peptide libraries such as the CX_7C library screened in Example 1 of the present application are utilized in order to identify smaller peptide motifs with a desired homing activity does not mean that only small peptides of less than about 10 amino acids will maintain the specificity of homing activity. The issue is whether one skilled in the art, based on the teachings in the specification and what was well known in the art, would understand how to make and use a peptide or conjugate comprising CREKA that would selectively home to tumor vasculature or selectively bind to collagen, and Applicants maintain that such teachings in the specification are sufficient. For example, as discussed above,

Applicants respectfully maintain that one skilled in the art could readily add one, two, three and so forth amino acids to a CREKA sequence, including up to a peptide having a length of less than 100 residues, as recited in the independent claims, and expect the peptide to have the recited activity of selectively homing to tumor vasculature or selectively binding to collagen.

The Office Action additionally asserts on page 11 that "the specification does not give enough direction or guideline to one skilled in the art that any peptide extending 6-95 amino acids from CREKA peptide could perform the same function as the CREKA because again, the activity in the peptides having a structure with up to 95% amino acid difference from the base sequence CREKA is unpredictable and would require undue experimentation and instant specification does not provide any example or objective evidence indicating that such claimed peptide would maintain the activity for tumor homing or collagen binding." Applicants respectfully disagree with the assertion that a 95% amino acid difference outside of the CREKA peptide sequence results in unpredictability. To the contrary, the CREKA sequence itself provides the functional activity of selective homing to tumor vasculature and selective binding to collagen. Therefore, contrary to the assertion in the Office Action, no undue experimentation would be required to add one, two, three, or more amino acids to a CREKA sequence, including up to a peptide having a length of less than 100 residues, and to screen for functional activity of selective homing to tumor vasculature or selective binding to collagen using the teachings in the specification and what was well known to those skilled in the art (see Examples 1 and 3).

For the reasons of record and as discussed above, Applicants respectfully maintain that the specification provides sufficient description and guidance to enable the claimed peptides and conjugates. Accordingly, Applicants respectfully request that this rejection be withdrawn.

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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